REMARKS

Claims 1, 4-7, 13 and 23-24 and 30-31 are pending. Claims 1 and 13 have been amended without prejudice to refiling of the original scope. Claims 30 and 31 are added. No new matter is added.

Support for the language of Claims 30 and 31 may be found in the language of originally filed Claims 4-5.

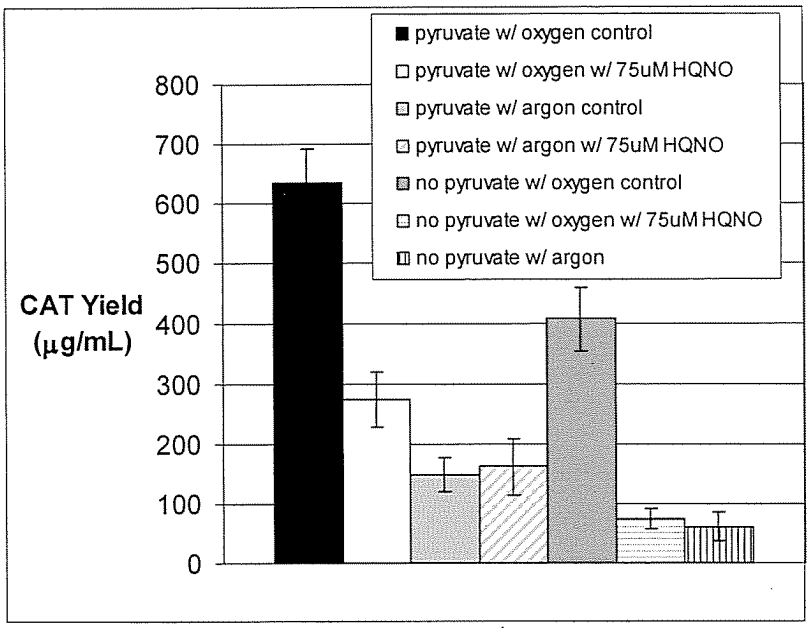
Claims 1, 3-7 and 13-24 have been rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The Office Action states while the specification describes the reaction mix prepared from *E. coli* grown under specific conditions, which result in activated oxidative phosphorylation, there is no disclosure of other types of reaction mixes having this property.

Without conceding to the correctness of the rejection, in order to further prosecution Applicants have amended independent Claims 1 and 13 to recite the use of *E. coli* extracts. In view of the amendments, withdrawal of the rejection is requested.

Claims 1, 4-7, 13, 23-24 have been rejected under 35 U.S.C. 103(a) as being unpatentable in view of Baranov *et al.* (1993) and Chen *et al.* in view of Yoshida *et al.*; Dorner *et al.*, Shimizu *et al.*, or Raney *et al.*

Applicants respectfully submit that the presently claimed invention is not made obvious by the cited art. Applicants respectfully submit that Baranov *et al.* fail to teach the activation of oxidative phosphorylation.

As set forth in Applicants' previous reply, the demonstration of oxidative phosphorylation is shown in the examples of the present application through a showing of polypeptide yield in the presence of absence of oxygen, and how inhibitors of the electron transport chain affect synthesis. In particular Applicants wish to point out the results shown in Figure 6, in which the reaction yields in the presence and absence of oxygen are shown.



It is evident from these data that where oxygen is not present, *i.e.* the head space is filled with the inert gas argon, the synthetic yield drops significantly. Clearly, in order to achieve *oxidative* phosphorylation, one must have oxygen present.

As previously discussed by Applicants, the activation of oxidative phosphorylation provides unexpected benefits, which could not have been predicted from the cited art. The methods of the invention provide for high levels of protein synthesis. For example, in Figure 2 it is shown that a yield of 700 µg/ml can be achieved using the glycolytic intermediate pyruvate as source of energy. Even in the absence of pyruvate, the methods as set forth in the present claims generated greater than 300 µg/ml polypeptide.

As demonstrated in Figure 6, it is the ability to activate oxidative phosphorylation that provides for such an increase in yield. Under conditions as set forth in the present claims, greater than 600 µg/ml of protein is produced in a batch reaction in the absence of a high energy phosphate source where oxygen is present (and thus where oxidative phosphorylation is activated), while in the presence of an electron transport chain inhibitor the yield drops to less than 300 µg/ml; and in the presence of argon (where no oxygen is present for oxidative phosphorylation) the yield drops to less than 150 µg/ml.

The unexpectedly high yields of the present invention may be compared to those of Baranov *et al.* The reaction mixture of Baranov *et al.*, although including a high energy phosphate source, does has some features in common with that of Applicants, as noted by the Examiner. However, the methods utilized by Baranov *et al.* provide a strikingly lower yield.

In spite of the presence of a high energy phosphate source, and in spite of providing the reaction with copious quantities of reagents during the feeding process, Baranov *et al.* were only able to obtain a total protein yield of 10 μg (presumably 20 μg/ml of starting reaction). Applicants are able to obtain 10 to 35 times greater yields (based on cell extract volume), using the presently claimed methods.

The question may be asked as to why Baranov *et al.* produced so little product? In answer, Applicants refer back to the requirement for oxygen in oxidative phosphorylation. As noted above, when the reaction is run in an inert gas, the yield drops significantly.

Baranov *et al.* fail to appreciate the role that oxygen might play in synthetic reactions, and indeed, teach a reactor process that will exclude oxygen and prevent oxidative phosphorylation from being activated.

Specifically, at page 124 of the reference, third paragraph under the heading *"Amicon 8MC Microultrafiltration System"*, Baranov *et al.* state:

> To prevent oxidation processes from occurring during incubation, the pressure of an inert gas (*e.g.* He_2) can be established in the incubation chamber and in the feeding solution reservoir. This pressure (about 0.5 to 2 additional atmospheres) can be used instead of the force pump. (underlining added)

Baranov *et al.* clearly teach away from the methods of the present invention. By teaching that one of skill in the art should provide an inert gas in the incubation chamber, Baranov *et al.* effectively prevent activation of oxidative phosphorylation, and any of the benefits that might have been provided by such activation. Indeed, it is a stated purpose to prevent oxidative processes.

Applicants respectfully submit that one of skill in the art could not have predicted that the reaction conditions set forth in the present claims would provide for the activation of oxidative phosphorylation, which provides for unexpected increase in synthetic yield. The cited art fails to appreciate the role of oxidative processes in energy generation, and specifically teaches the use of reaction conditions that would present oxidative phosphorylation.

The secondary references fail to remedy the deficiencies of the primary reference. The Office Action states that Yoshida *et al.* (1999); Dorner *et al.* (1979), Shimizu *et al.* or Raney *et al.* (2000) disclose *in vitro* translation systems in which spermidine is present at a concentration of about 1 mM. It is asserted that it would have been obvious to vary the spermidine concentration in order to optimize conditions.

Applicants respectfully submit that altering the methods of Baranov *et al.* to optimize spermidine concentration would not have resulted in a system where oxidative phosphorylation was activated, because Baranov *et al.* teach that oxidation processes are undesirable, and that it is desirable to prevent oxidative processes by excluding oxygen from the incubation chamber. The combined teachings of the references would therefore fail to provide the methods set forth in the present claims.

In view of the above remarks, Applicants respectfully submit that the present claims are not taught or suggested by the cited art. Withdrawal of the rejection is requested.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-273.

Respectfully submitted,
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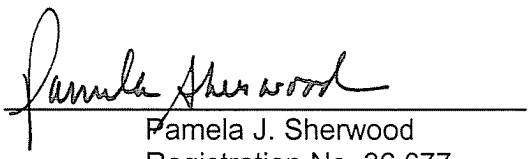
By: 
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